EXHIBIT F

THE CLAIMS

What is claimed is:

1. An oral dosage form which weighs about 62.5 mg and comprises: 1) pomolidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 0.5 mg potency of pomolidomide; and 2) a pharmaceutically acceptable carrier or excipient.

2. The dosage form of claim 1, wherein the carrier or excipient comprises starch.

3. The dosage form of claim 2, wherein the starch is pregelatinized starch.

4. The dosage form of claim 3, wherein the pregelatinized starch is present at an amount of about 35 mg.

5. The dosage form of claim 1, wherein the carrier or excipient comprises sodium stearyl fumarate.

6. The dosage form of claim 5, wherein the sodium stearyl fumarate is present at an amount of about 0.16 mg.

7. The dosage form of claim 1, wherein the carrier or excipient comprises mannitol.

8. The dosage form of claim 7, wherein the mannitol is spray dried mannitol.

9. The dosage form of claim 8, wherein the spray dried mannitol is present at an amount that brings the total weight of the composition to about 62.5 mg.

10. The dosage form of claim 1, which is to be administered in the form of a size 4 or larger capsule.

11. An oral dosage form which weighs about 125 mg and comprises: 1) pomolidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that

provides 1 mg potency of pomolidomide; and 2) a pharmaceutically acceptable carrier or excipient.

12. The dosage form of claim 11, wherein the carrier or excipient comprises starch.

13. The dosage form of claim 12, wherein the starch is pregelatinized starch.

14. The dosage form of claim 13, wherein the pregelatinized starch is present at an amount of about 70 mg.

15. The dosage form of claim 11, wherein the carrier or excipient comprises sodium stearyl fumarate.

16. The dosage form of claim 15, wherein the sodium stearyl fumarate is present at an amount of about 0.32 mg.

17. The dosage form of claim 11, wherein the carrier or excipient comprises mannitol.

18. The dosage form of claim 17, wherein the mannitol is spray dried mannitol.

19. The dosage form of claim 18, wherein the spray dried mannitol is present at an amount that brings the total weight of the composition to about 125 mg.

20. The dosage form of claim 11, which is to be administered in the form of a size 4 or larger capsule.

21. An oral dosage form which weighs about 250 mg and comprises: 1) pomolidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 2 mg potency of pomolidomide; and 2) a pharmaceutically acceptable carrier or excipient.

22. The dosage form of claim 21, wherein the carrier or excipient comprises starch.

23. The dosage form of claim 22, wherein the starch is pregelatinized starch.

24. The dosage form of claim 23, wherein the pregelatinized starch is present at an amount of about 140 mg.

25. The dosage form of claim 21, wherein the carrier or excipient comprises sodium stearyl fumarate.

26. The dosage form of claim 25, wherein the sodium stearyl fumarate is present at an amount of about 0.64 mg.

27. The dosage form of claim 21, wherein the carrier or excipient comprises mannitol.

28. The dosage form of claim 27, wherein the mannitol is spray dried mannitol.

29. The dosage form of claim 28, wherein the spray dried mannitol is present at an amount that brings the total weight of the composition to about 250 mg.

30. The dosage form of claim 21, which is to be administered in the form of a size 2 or larger capsule.

31. An oral dosage form which weighs about 180 mg and comprises: 1) pomolidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 3 mg potency of pomolidomide; and 2) a pharmaceutically acceptable carrier or excipient.

32. The dosage form of claim 31, wherein the carrier or excipient comprises starch.

33. The dosage form of claim 32, wherein the starch is pregelatinized starch.

34. The dosage form of claim 33, wherein the pregelatinized starch is present at an amount of about 100 mg.

35. The dosage form of claim 31, wherein the carrier or excipient comprises sodium stearyl fumarate.

36. The dosage form of claim 35, wherein the sodium stearyl fumarate is present at an amount of about 0.45 mg.

37. The dosage form of claim 31, wherein the carrier or excipient comprises mannitol.

38. The dosage form of claim 37, wherein the mannitol is spray dried mannitol.

39. The dosage form of claim 38, wherein the spray dried mannitol is present at an amount that brings the total weight of the composition to about 180 mg.

40. The dosage form of claim 31, which is to be administered in the form of a size 2 or larger capsule.

41. An oral dosage form which weighs about 240 mg and comprises: 1) pomolidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 4 mg potency of pomolidomide; and 2) a pharmaceutically acceptable carrier or excipient.

42. The dosage form of claim 41, wherein the carrier or excipient comprises starch.

43. The dosage form of claim 42, wherein the starch is pregelatinized starch.

44. The dosage form of claim 43, wherein the pregelatinized starch is present at an amount of about 135 mg.

45. The dosage form of claim 41, wherein the carrier or excipient comprises sodium stearyl fumarate.

46. The dosage form of claim 45, wherein the sodium stearyl fumarate is present at an amount of about 0.6 mg.

47. The dosage form of claim 41, wherein the carrier or excipient comprises mannitol.

48. The dosage form of claim 47, wherein the mannitol is spray dried mannitol.

49. The dosage form of claim 48, wherein the spray dried mannitol is present at an amount that brings the total weight of the composition to about 240 mg.

50. The dosage form of claim 41, which is to be administered in the form of a size 2 or larger capsule.

51. An oral dosage form which weighs about 300 mg and comprises: 1) pomolidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 5 mg potency of pomolidomide; and 2) a pharmaceutically acceptable carrier or excipient.

52. The dosage form of claim 51, wherein the carrier or excipient comprises starch.

53. The dosage form of claim 52, wherein the starch is pregelatinized starch.

54. The dosage form of claim 53, wherein the pregelatinized starch is present at an amount of about 168 mg.

55. The dosage form of claim 51, wherein the carrier or excipient comprises sodium stearyl fumarate.

56. The dosage form of claim 55, wherein the sodium stearyl fumarate is present at an amount of about 0.75 mg.

57. The dosage form of claim 51, wherein the carrier or excipient comprises mannitol.

58. The dosage form of claim 57, wherein the mannitol is spray dried mannitol.

59. The dosage form of claim 58, wherein the spray dried mannitol is present at an amount that brings the total weight of the composition to about 300 mg.

60. The dosage form of claim 51, which is to be administered in the form of a size 1 or larger capsule.

DETAILED ACTION

This application claims priority from provisional application 61/179678 filed 05/19/2009. Claims 1-60 are currently pending in the application and are examined on the merits.

Claim Interpretation

The claims contain the term "about" in front of quantities of active agent and excipients. Based on the specification the term "about" is defined as a dose, amount, or weight percent within 30%, 25%, 20%, 15%, 10%, or 5% of the specified dose, amount, or weight percent (Page 5 lines 3-9). Therefore, the claimed amounts of active and excipients are viewed as ranges.

Claim Objections

Claims 1, 11, 21, 31, 41, and 51 are objected to because of the following informalities: The claims recite pomolidomide. The search of the term "pomolidomide" retrieved applicant's instant application only. The compound 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione is known in the art as pomalidomide. Did applicant mean pomalidomide?

Appropriate correction is required.

Claim Rejections – 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11, 21, 31, 41, and 51 are indefinite because they recite potency of pomalidomide in miligrams. Potency of a drug is expressed in International Units (IU) and not mass. For the purpose of applying prior art, mg potency is treated as mg of drug present in a formulation.

Claims 2-10, 12-20, 22-30, 32-40, 42-50, and 52-60 are indefinite because they depend from indefinite claims.

Appropriate correction is required.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7, 11-14, 17, 21-24, 27, 31-34, 37, 41-44, 47, 51-54, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeldis et al. (Pub. No. US 2007/0155791 A1, Published July 5, 2007).

The claims encompass an oral dosage form which comprises pomalidomide and a pharmaceutically acceptable carrier or excipient.

The teachings of Zeldis et al. are related to methods for treating lupus and compositions comprising 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione (e.g. pomalidomide) (Abstract). In one embodiment pomalidomide is administered daily at a dose of from about 0.1 to 5 mg per day (Paragraph 0096). In one embodiment, pomalidomide can be administered in an amount from about 0.1 to about 100 mg. In a particular embodiment polamidomide may be administered in an amount of froma bout 0.1 to about 2 mg per day, or from 0.1 to about 5 mg every other day (Paragraph 0102). Typical dosage forms comprise pomalidomide in an amount from about 0.1 to about 150 mg (Paragraph 0106). Single unit dosage forms are suitable for oral administration, including capsules (Paragraph 0109). The composition and type of dosage form will vary depending on its use. For example, a dosage form used in the acute treatment of a disease may contain larger amount of active ingredient than a dosage form used in the chronic treatment of the same disease (Paragraph 0110). Typical dosage forms comprise excipients (Paragraph 0111). Oral dosage forms, such as capsules, contain a predetermined amount of active ingredients and can be prepared by methods well known in the art (Paragraph 0118).

Excipients suitable for use in solid oral dosage forms include starches, sugars, diluents, lubricants, and binders (Paragraph 0119). Pre-gelatinized starch is an example of binder (Paragraph 0122). Suitable fillers include mannitol and pre-gelatinized starch and mixtures thereof. The binder or filler in pharmaceutical composition is typically present in from about 50 to about 99 weight percent of the dosage from (Paragraph 0124). The compositions comprise from about 0.5 to about 15 wt. % disintegrants (Paragraph 0125). Pre-gelatinized starch is an example of a disintegrant (Paragraph 0126).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have made oral dosage forms comprising pomalidomide and excipients such as mannitol and pre-gelatinized starch, with a reasonable expectation of success because Zeldis et al. taught such oral dosage forms. It would have been obvious to optimize the concentration of pomalidomide and excipients because the claimed ranges overlap with the ranges disclosed by Zeldis et al. MPEP 2144.05(I) states in the case where the claimed ranges overlap or lie inside ranges disclosed by the prior art a *prima facie* case of obviousness exist. It would have been obvious to make single unit dosage forms that contain predetermined amounts of active in the range of from about 0.1 mg to about 5 mg, with a reasonable expectation of success because Zeldis et al. taught discrete single unit dosage forms that contain predetermined amounts of drug in the range from about 0.1 mg to about 5 mg. A person of ordinary skill in the art is capable of determining appropriate quantities of drug per dosage form depending on its intended use and the quantity of drug that is required to treat a particular patient.

Regarding claims 1, 11, and 21, Zeldis et al. taught that typical dosage forms contain from about 50% to about 99% of fillers or binders, and from about 0.5 to about 15 wt. % disintegrant. Therefore, the remainder of the composition (from about 49.5% to about 0.5%) must be pomalidomide. The composition in claim 1 weighs about 62.5 mg of which 0.5 mg is pomalidomide; the composition in claim 11 weighs about 125 mg of which 1 mg is pomalidomide; and the composition in claim 21 weighs about 250 mg of which 2 mg is pomalidomide; therefore the compositions in claims 1, 11, and 21 contain pomalidomide in a concentration of about 0.8 wt. % and excipient in a concentration of about 99.2%, which overlap the ranges of the prior art. Furthermore, Zeldis et al. taught that pomalidomide may be administered in an amount from about 0.1 mg to about 5 mg per day. The claimed amount of drug is within this range.

Regarding claims 31, 41, and 51, Zeldis et al. taught that typical dosage forms contain from about 50% to about 99% of fillers or binders, and from about 0.5 to about 15 wt. % disintegrant. Therefore, the remainder of the composition (from about 49.5% to about 0.5%) must be pomalidomide. The composition in claim 31 weighs about 180 mg of which 3 mg is pomalidomide; the composition in claim 41 weighs about 240 mg of which 4 mg is pomalidomide; the composition in claim 51 weighs about 300 mg of which 5 mg is pomalidomide; therefore compositions in claims 31, 41, and 51 contain pomalidomide in a concentration of about 1.7 wt. % and excipients in a concentration of about 98.3%, which overlap the ranges of the prior art. Furthermore, Zeldis et al. taught that pomalidomide may be administered in an amount from about 0.1 mg to about 5 mg per day. The claimed amount of drug is within this range.

Regarding claims 4, 14, 24, 34, 44, and 54, Zeldis et al. taught that typical dosage forms contain from about 50% to about 99% of fillers or binders. The claimed compositions contain about 56% of pre-gelatinized starch (binder). The claimed range of pre-gelatinized starch overlaps with the range of the prior art.

Claims 8-10, 18-20, 28-30, 38-40, 48-50, and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeldis et al. as applied to claims 1-4, 7, 11-14, 17, 21-24, 27, 31-34, 37, 41-44, 47, 51-54, and 57 above, and further in view of Remington's Pharmaceutical Sciences 17th Edition, Published 1985, Pages 1613-1615 and 1625-1626.

The claims encompass the dosage form of claim 1 which administered in the form of a size 4 or larger capsule, the dosage form of claim 11 which administered in the form of a size 4 or larger capsule, the dosage form of claim 21 which administered in the form of a size 2 or larger capsule, the dosage form of claim 31 which administered in the form of a size 2 or larger capsule, the dosage form of claim 41 which administered in the form of a size 2 or larger capsule, and the dosage form of claim 51 which administered in the form of a size 1 or larger capsule. The claims encompass dosage forms of claims 7, 17, 27, 37, 47, and 57 wherein mannitol is spray-dried mannitol.

The teachings of Zeldis et al. are relied upon as summarized above.

Regarding claims 10, 20, 30, 40, 50 and 60, although Zeldis et al. taught that the oral dosage forms are advantageously administered in capsule form, they are silent regarding capsule sizes that should be utilized.

Remington's discloses various capsule sizes (Page 1625, Right Column, Fig. 90-30). The capsules are numbered from 000, the largest size which can be swallowed, to 5, which is the smallest. The approximate capacity for capsules from 000 to 5 ranges from 600 mg to 30 mg, although this will vary because of the different densities of powdered drug material (Page 1626, Left Column, First Paragraph).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have made the dosage forms of Zeldis et al. in the capsule form using the capsule sizes disclosed Remington's, with a reasonable expectation of success because Remington's discloses capsule capacities and sizes that are used to deliver pharmaceuticals. One of ordinary skill would have been able to determine which capsule size is appropriate for a particular dosage amount (e.g. smaller capsule size for a small dosage, larger capsule size for a large dosage) because Remington's provides capsule capacities.

Regarding claims 8, 18, 28, 38, 48, and 58, although Zeldis et al. taught mannitol as excipient, they are silent whether or not it is spray-dried mannitol.

Remington's discloses that direct compression for tablets containing less than 25% of drug substance can be used by formulation with a suitable diluent which acts as a carrier (Page 1614, Left Column, First Paragraph). Direct-compression carriers must have good flow and compressible characteristics. These properties are imparted to them by a processing step such as

spray-drying. These carriers include processed forms of the most common diluents including mannitol (Page 1614, Left Column, Third Paragraph). Spray-dried powder particles are homogeneous, spherical shape, nearly uniform in size, and frequently hallow. The latter characteristic results in low bulk density with a rapid dissolution rate. Being uniform in size and spherical, the particles possess good flowability. Among the spray-dried materials available for direct compression formulas are lactose, mannitol and flour (Page 1615, Left Column, First Paragraph). Spray-drying is more economical than other processes since it produces a dry powder directly from a liquid and eliminates other processing steps. By the elimination of additional steps, labor, equipment cost, space requirements, and possible contamination of the product are reduced (Page 1615, Left Column, Third Paragraph).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have prepared the dosage forms of Zeldis et al. in the form of a tablet utilizing spray-dried mannitol, with a reasonable expectation of success because Remington's discloses that spray-dried carriers (mannitol) have good flowability and compressability which are desired characteristics in direct-compression carriers utilized in making tablets. Remington's also discloses that spray-drying is more economical than other processes, which provides motivation to process mannitol by spray-drying.

Regarding claims 9, 19, 29, 39, 49, and 59, Zeldis et al. taught that typical dosage forms contain from about 50% to about 99% of fillers or binders. The concentration of excipient in claims 9, 19, 29, is about 99.2%; and the concentration of excipient in claims 39, 49, and 59 is about 98.3%. The claimed concentration ranges of the excipient overlap with the concentration ranges disclosed by Zeldis et al. Therefore, the claimed concentration ranges of excipients are

obvious, since it has been held that in the case where the claimed ranges overlap or lie inside ranges disclosed by the prior art a *prima facie* case of obviousness exist.

Claims 5, 6, 15, 16, 25, 26, 35, 36, 45, 46, 55, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeldis et al. as applied to claims 1-4, 7, 11-14, 17, 21-24, 27, 31-34, 37, 41-44, 47, 51-54, and 57 above, and further in view of McNally et al. (Patent No. 5,593,696 Date of Patent January 14, 1997).

The claims encompass the dosage forms of claims 1, 11, 21, 31, 41, and 51, wherein the carrier or excipient comprises sodium stearyl fumarate.

The teachings of Zeldis et al. are relied upon as summarized above. Although they teach incorporating lubricants such as magnesium stearate, calcium stearate, stearic acid, and talc in an amount of less than 1% by weight of the composition (paragraph 0127), they do not teach the specific lubricant sodium stearyl fumarate.

The teachings of McNally et al. are relied upon to show that sodium stearyl fumarate is a known lubricant in the art, and that it is an art recognized equivalent of magnesium stearate, calcium stearate, stearic acid, and talc in oral pharmaceutical dosage forms (Column 4, lines 27-32). The teachings of McNally et al. are related to oral dosage forms comprising an active ingredient (Abstract).

A person of ordinary skill in the art would have been motivated to combine the teachings of Zeldis et al. and McNally et al. because both are related to oral dosage forms that contain an active agent and excipients. It would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have modified the dosage forms of Zeldis et al. by

substituting lubricants magnesium stearate, calcium stearate, stearic acid, and talc with sodium stearyl fumarate, with a reasonable expectation of success because according to McNally et al. sodium stearyl fumarate, magnesium stearate, calcium stearate, stearic acid, and talc are art recognized equivalent lubricants in oral dosage forms.

Regarding claims 6, 16, 26, 36, 46, and 56, Zeldis et al. taught that lubricant should be present in an amount of less than 1% by weight of the composition. In the claimed compositions, sodium stearyl fumarate is present in a concentration of about 0.25%, which is encompassed by the range of the prior art. The claimed concentration range is obvious since it has been held that in the case where the claimed ranges overlap or lie inside ranges disclosed by the prior art a *prima facie* case of obviousness exist.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALMA PIPIC whose telephone number is (571)270-7459. The examiner can normally be reached on 8-5 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on (571) 272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

LISTING OF CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently amended) An oral dosage form which weighs about 62.5 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 35 mg; 3) sodium stearyl fumarate at an amount of 0.16 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 62.5 mg.

2-9. (Canceled).

10. (Previously presented) The dosage form of claim 1, which is to be administered in the form of a size 4 or larger capsule.

11. (Currently Amended). An oral dosage form which weighs about 125 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 70 mg; 3) sodium stearyl fumarate at an amount of 0.32 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 125 mg.

12-19. (Canceled).

20. (Previously presented) The dosage form of claim 11, which is to be administered in the form of a size 4 or larger capsule.

21. (Currently amended) An oral dosage form which weighs about 250 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a~~

~~pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 140 mg; 3) sodium stearyl fumarate at an amount of 0.64 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 250 mg.

22-29. (Canceled)

30. (Previously presented) The dosage form of claim 21, which is to be administered in the form of a size 2 or larger capsule.

31. (Currently amended) An oral dosage form which weighs about 180 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 100.8 mg; 3) sodium stearyl fumarate at an amount of 0.45 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 180 mg.

40. (Previously presented) The dosage form of claim 31, which is to be administered in the form of a size 2 or larger capsule.

41. (Currently amended) An oral dosage form which weighs about 240 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 134.4 mg; 3) sodium stearyl fumarate at an amount of 0.6 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 240 mg.

42-49. (Canceled).

50. (Previously presented) The dosage form of claim 41, which is to be administered in the form of a size 2 or larger capsule.

51. (Currently amended) An oral dosage form which weighs about 300 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 168 mg; 3) sodium stearyl fumarate at an amount of 0.75 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 300 mg.

52-59. (Canceled)

60. (Previously presented) The dosage form of claim 51, which is to be administered in the form of a size 1 or larger capsule.

61. (New) An oral dosage form in the form of a capsule which comprises: 1) pomalidomide at an amount of 0.1 to 3 weight percent of the total weight of the composition; 2) a binder or filler at an amount of 90 to 99 weight percent of total weight of the composition, wherein the binder or filler is starch, mannitol or a mixture thereof.

62. (New) The oral dosage form of claim 61, wherein pomalidomide is present at an amount of 0.5 to 2 weight percent of total weight of the composition.

63. (New) The oral dosage form of claim 61, wherein the binder or filler is present at an amount of 95 to 99 weight percent of total weight of the composition.

64. (New) The oral dosage form of claim 61, wherein the binder or filler is a mixture of starch and mannitol.

65. (New) The oral dosage form of claim 64, wherein the starch is pregleatinized starch.

66. (New) The oral dosage form of claim 64, wherein the mannitol is spray dried mannitol.

67. (New) The oral dosage form of claim 61 further comprising a lubricant at an amount of 0.01 to 1 weight percent of total weight of the composition.

68. (New) The oral dosage form of claim 7, wherein the lubricant is present at an amount of 0.1 to 0.5 weight percent of total weight of the composition.

69. (New) The oral dosage form of claim 7 or 8, wherein the lubricant is sodium stearyl fumarate.

REMARKS

Upon entry of the specification and claim amendments presented herein, claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, and 60-69 are pending in the present application. Claims 2-9, 12-19, 22-29, 32-39, 42-49, and 52-59 are canceled without prejudice to Applicants' right to pursue any canceled subject matter in one or more divisional, continuation, and/or continuation-in-part applications. The specification and claims 1, 11, 21, 31, 41, and 51 are amended to replace all recitations of "pomolidomide" with "pomalidomide" solely to correct informalities alleged by the Examiner. Claims 1, 11, 21, 31, 41, and 51 are further amended to recite more precisely the compositions of the claimed oral dosage forms. Support for amended claim 1 can be found, for example, on page 10, lines 15-21 of the present specification. Support for amended claim 11 can be found, for example, on page 11, lines 5-11 of the present specification. Support for amended claim 21 can be found, for example, on page 11, line 30 to page 12, line 2 of the present specification. Support for amended claim 31 can be found, for example, on page 12, lines 21-27 of the present specification. Support for amended claim 41 can be found, for example, on page 13, lines 10-16 of the present specification. Support for amended claim 51 can be found, for example, on page 14, lines 1-7 of the present specification.

New claims 61-69 are added. Support for new claim 61 can be found at page 7, lines 26-29 of the present specification. Support for new claim 62 can be found at page 7, lines 31-34 of the present specification. Support for new claim 63 can be found at page 8, lines 20-22 of the present specification. Support for new claim 64 can be found at page 8, line 26 to page 9, line 2 of the present specification. Support for new claims 65-66 can be found at page 8, lines 9-13 of the present specification. Support for new claim 67 can be found at page 9, lines 6-9 of the present specification. Support for new claim 68 can be found at page 9, lines 14-16 of the present specification. Support for new claim 69 can be found at page 9, line 9 of the present specification. No new matter is added.

Applicants respectfully submit that all of the pending claims are allowable for at least the reasons set forth below.

DETAILED ACTION

Applicant's response dated 08/16/2012 to the non-final rejection dated 04/24/2012 is acknowledged.

Priority

This application claims priority from provisional application 61/179,678 filed 05/19/2009.

Claim Status

Claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, 60-69 are currently pending in the application and are examined on the merits. Claims 2-9, 12-19, 22-29, 32-39, 42-49, and 52-59 have been cancelled. Claims 1, 11, 21, 31, 41, and 51 have been amended. Claims 61-69 have been newly added.

Withdrawn Claim Objections

Claim amendments filed 08/16/2012 overcame the objections to claims 1, 11, 21, 31, 41, and 51.

New Claim Objections

The claim listing is objected to because claim amendments filed 08/16/2012 are not in compliance with 37 CFR 1.121 or 1.4. Specifically, claims 32-39 are missing from the claim amendment. In the arguments, applicant indicated that claims 32-39 have been cancelled, however they are not listed as cancelled in the amendment. Claim 1 is not properly marked up. The previously presented claim 1 recites "0.5 mg potency", whereas the currently amended claim 1 recites "1 mg potency" wherein the "1" is not underlined and "0.5" is not stricken through. Claim 21 is not properly marked up. The previously presented claim 21 recites "2 mg potency",

whereas the currently amended claim 21 recites "1 mg potency" wherein the "1" is not underlined and "2" is not stricken through. Claim 31 is not properly marked up. The previously presented claim 31 recites "3 mg potency", whereas the currently amended claim 31 recites "1 mg potency" wherein the "1" is not underlined and "3" is not stricken through. Claim 41 is not properly marked up. The previously presented claim 41 recites "4 mg potency", whereas the currently amended claim 41 recites "1 mg potency" wherein the "1" is not underlined and "4" is not stricken through. Claim 51 is not properly marked up. The previously presented claim 51 recites "5 mg potency", whereas the currently amended claim 51 recites "1 mg potency" wherein the "1" is not underlined and "5" is not stricken through.

Claim 65 objected to because of the following informalities: In claim 65 "pregleatinized" is misspelled and should be "pregelatinized".

Appropriate correction is required.

New Claim Rejections – 35 USC § 112, 1st Paragraph, New Matter – Necessitated by Amendment

The following is a quotation of 35 U.S.C. 112(a):
(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10, 21, 30, 31, 40, 41, 50, 51, and 60 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. Claimed embodiments are not supported by the specification as originally filed. There is no support in the specification for oral dosage forms that weigh about 62.5 mg, about 250 mg, about, about 180 mg, about 240 mg, and about 300 mg and each comprise an amount of pomalidomide that provides 1 mg potency.

Claim Rejections – 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11, 21, 31, 41, and 51 are indefinite because they recite potency of pomalidomide in miligrams. Potency of a drug is expressed in International Units (IU) and not mass. For the purpose of applying prior art, mg potency is treated as mg of drug present in a formulation.

Claims 10, 20, 30, 40, 50, and 60 are indefinite because they depend from indefinite claims.

Applicant's arguments filed 08/16/2012 (page 8, item B) have been fully considered but were not found persuasive because potency was not redefined by the specification and it is given its plain and ordinary meaning. Potency is a measure of an amount of drug necessary to produce an effect of a given magnitude. In the instant case the effect and the magnitude of the said effect are unknown and thus the amount of pamolidamide required to give a potency of 1 mg cannot be determined since it remains unknown what effect one is trying to achieve. A 1 mg of a drug will have different effect on a mouse in comparison to an effect it has on an adult human. Since the subject and the effect that one is trying to achieve on the subject are unknown, one cannot determine the amount of pomalidomide that would product 1 mg worth of potency. Based on the specification (from page 9 line 30 to page 10 line 5) it appears that the applicant intended to say that since pomalidomide is obtained at a purity of less than 100%, the amount of impure pamolidomide that is utilized in the dosage forms should provide a specified amount of pure pamolidomide such as 0.5 mg. Thus, the term "1 mg potency" renders the claims indefinite and for the purpose of applying prior art the claims are interpreted as requiring 1 mg of pamolidomide.

Appropriate correction is required.

Claim Rejections – 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, 60, and 61-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeldis et al. (Pub. No. US 2007/0155791 A1, Published July 5, 2007 – of record in PTO-892 dated 04/24/2012) in view of Remington's Pharmaceutical Sciences (17th Edition, Published 1985, Pages 1613-1615 and 1625-1626 - of record in PTO-892 dated 04/24/2012) and McNally et al. (Patent No. 5,593,696 Date of Patent January 14, 1997 - of record in PTO-892 dated 04/24/2012).

Claim 1 encompasses an oral dosage form which weighs about 62.5 mg and comprises: 1) pomalidomide in an amount of 1 mg; 2) pregelatinized starch in an amount of 35 mg; 3) sodium stearyl fumarate in an amount of 0.16 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 62.5 mg.

Claim 11 encompasses an oral dosage form which weighs about 125 mg and comprises: 1) pomalidomide in an amount of 1 mg; 2) pregelatinized starch in an amount of 70 mg; 3) sodium stearyl fumarate in an amount of 0.32 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 125 mg.

Claim 21 encompasses an oral dosage form which weighs about 250 mg and comprises: 1) pomalidomide in an amount of 1 mg; 2) pregelatinized starch in an amount of 140 mg; 3) sodium stearyl fumarate in an amount of 0.64 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 250 mg.

Claim 31 encompasses an oral dosage form which weighs about 180 mg and comprises: 1) pomalidomide in an amount of 1 mg; 2) pregelatinized starch in an amount of 100.8 mg; 3) sodium stearyl fumarate in an amount of 0.45 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 180 mg.

Claim 41 encompasses an oral dosage form which weighs about 240 mg and comprises: 1) pomalidomide in an amount of 1 mg; 2) pregelatinized starch in an amount of 134.4 mg; 3) sodium stearyl fumarate in an amount of 0.6 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 240 mg.

Claim 51 encompasses an oral dosage form which weighs about 300 mg and comprises: 1) pomalidomide in an amount of 1 mg; 2) pregelatinized starch in an amount of 168 mg; 3) sodium stearyl fumarate in an amount of 0.75 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 300 mg.

Claim 61 encompasses an oral dosage form in the form of a capsule which comprises: 1) pomalidomide at an amount of 0.1 to 3 weight percent of the total weight of the composition; 2) a binder or filler at an amount of 90 to 99 weight percent of total weight of the composition, wherein the binder or filler is starch, mannitol or a mixture thereof. Dependent claim 62 requires pomalidomide at an amount of 0.5 to 2 weight percent of total weight of the composition. Dependent claim 63 requires the binder or filler at an amount of 95 to 99 weight percent of total

weight of the composition. Dependent claims 64-66 require that the binder or filler is a mixture of starch and mannitol, wherein the starch is pregelatinized starch and mannitol is spray dried mannitol. Depended claims 67-69 require a lubricant at an amount of 0.01 to 1 weight percent and 0.1 to 0.5 weight percent of the total weight of the composition, wherein the lubricant is sodium stearyl fumarate.

The teachings of Zeldis et al. are related to methods for treating lupus and compositions comprising 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione (e.g. pomalidomide) (Abstract). In one embodiment pomalidomide is administered daily at a dose of from about 0.1 to 5 mg per day (Paragraph 0096). In one embodiment, pomalidomide can be administered in an amount from about 0.1 to about 100 mg. In a particular embodiment polamidomide may be administered in an amount of from about 0.1 to about 2 mg per day, or from 0.1 to about 5 mg every other day (Paragraph 0102). Typical dosage forms comprise pomalidomide in an amount from about 0.1 to about 150 mg (Paragraph 0106). Single unit dosage forms are suitable for oral administration, including capsules (Paragraph 0109). The composition and type of dosage form will vary depending on its use. For example, a dosage form used in the acute treatment of a disease may contain larger amount of active ingredient than a dosage form used in the chronic treatment of the same disease (Paragraph 0110). Typical dosage forms comprise excipients (Paragraph 0111). Oral dosage forms, such as capsules, contain a predetermined amount of active ingredients and can be prepared by methods well known in the art (Paragraph 0118). Excipients suitable for use in solid oral dosage forms include starches, sugars, diluents, lubricants, and binders (Paragraph 0119). Pre-gelatinized starch is an example of binder

(Paragraph 0122). Suitable fillers include mannitol and pre-gelatinized starch and mixtures thereof. The binder or filler in pharmaceutical composition is typically present in from about 50 to about 99 wt. % of the dosage from (Paragraph 0124). The compositions comprise from about 0.5 to about 15 wt. % disintegrants (Paragraph 0125).

Although Zeldis et al. taught mannitol as excipient, they are silent whether or not it is spray-dried mannitol.

Remington's discloses that direct compression for tablets containing less than 25% of drug substance can be used by formulation with a suitable diluent which acts as a carrier (Page 1614, Left Column, First Paragraph). Among the spray-dried materials available for direct compression formulas are lactose, mannitol and flour (Page 1615, Left Column, First Paragraph). Spray-drying is more economical than other processes since it produces a dry powder directly from a liquid and eliminates other processing steps. By the elimination of additional steps, labor, equipment cost, space requirements, and possible contamination of the product are reduced (Page 1615, Left Column, Third Paragraph).

Although Zeldis et al. taught that the oral dosage forms are advantageously administered in capsule form, they are silent regarding capsule sizes that should be utilized.

Remington's discloses various capsule sizes (Page 1625, Right Column, Fig. 90-30). The capsules are numbered from 000, the largest size which can be swallowed, to 5, which is the smallest. The approximate capacity for capsules from 000 to 5 ranges from 600 mg to 30 mg, although this will vary because of the different densities of powdered drug material (Page 1626, Left Column, First Paragraph) (Relevant to claims 10, 20, 30, 40, 50, and 60).

Although Zeldis taught incorporating lubricants such as magnesium stearate, calcium stearate, stearic acid, and talc in an amount of less than 1% by weight of the composition (paragraph 0127), they do not teach lubricant sodium stearyl fumarate.

The teachings of McNally et al. are relied upon to show that sodium stearyl fumarate is a known lubricant in the art, and that it is an art recognized equivalent of magnesium stearate, calcium stearate, stearic acid, and talc in oral pharmaceutical dosage forms (Column 4, lines 27-32). The teachings of McNally et al. are related to oral dosage forms (Abstract).

A person of ordinary skill in the art would have been motivated to combine the teachings of Zeldis et al., McNally et al., and Remington's because they are related to oral dosage forms that contain an active agent and excipients. It would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have followed the teachings of Zeldis and made oral dosages in the form of capsules comprising 0.1-2 mg of pamolidomide as the active, a mixture of pre-gelatinized starch and mannitol as filler and binder, and lubricant in order to form a dosage form suitable for treatment of a chronic disease, with a reasonable expectation of success because Zeldis taught oral dosage forms comprising those components and suggested using an amount of the active in the lower end of the range in order to treat a chronic disease. It would have been obvious to have selected a mixture of pre-gelatinized starch and mannitol as filler and binder because Zeldis taught that they are suitable for that use. It would have been obvious to have modified Zeldis' oral dosage forms by substituting lubricants magnesium stearate, calcium stearate, stearic acid, or talc with sodium stearyl fumarate, with a reasonable expectation of success because sodium stearyl fumarate, magnesium stearate, calcium

stearate, stearic acid, and talc are recognized in the art as equivalent lubricants in oral dosage forms according to McNally et al. A person of ordinary skill would have been motivated to use spray dried mannitol because Remington's discloses that spray drying of excipients is more economical than other processes since it produces a dry powder directly from a liquid and eliminates other processing steps. By the elimination of additional steps, labor, equipment cost, space requirements, and possible contamination of the product are reduced. It would have been obvious to make single unit dosage forms that contain predetermined amounts of active such as 1 mg, with a reasonable expectation of success because Zeldis et al. taught discrete single unit dosage forms that contain predetermined amounts of drug in the range from about 0.1 mg to about 2 mg. A person of ordinary skill in the art is capable of determining appropriate quantities of drug per dosage form depending on its intended use and the quantity of drug that is required to treat a particular patient as well as amounts of suitable excipients. The claimed ranges of pomalidomide, pre-gelatinized starch, and sodium stearyl fumarate are obvious over Zeldis et al. in view of McNally and Remington's since it has been held where the claimed ranges overlap or lie inside ranges disclosed by the prior art a *prima facie* case of obviousness exist (MPEP 2144.05(I)). The claimed amount of spray dried mannitol (about 43 wt. %) is obvious over the prior art range (about 50-99 wt. %) since it has been held that a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties (MPEP 2144.05(I)). It would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have made the dosage forms of Zeldis et al. in the capsule form using the capsule sizes disclosed Remington's, with a reasonable expectation of success because Remington's

discloses capsule capacities and sizes that are used to deliver pharmaceuticals. One of ordinary skill would have been able to determine which capsule size is appropriate for a particular dosage amount (e.g. smaller capsule size for a small dosage, larger capsule size for a large dosage) because Remington's provides capsule capacities as ranging from 30 mg to 600 mg. The claimed weights of dosage forms 62.5 mg, 125 mg, 250 mg, 180 mg, 240 mg, and 300 mg are obvious over Remington's because they overlap with the range of amounts (30-600 mg) that the standard size capsules are capable of holding. One of ordinary skill is capable of determining the weight of a dosage form that is suitable for a particular capsule size.

Regarding claims 1, 11, 21, 31, 41, 51, 61-63, 67, and 68, Zeldis et al. taught that typical dosage forms contain from about 50% to about 99% of fillers or binders, from about 0.5 to about 15 wt. % disintegrant, and less than 1 wt. % lubricant. Therefore, the remainder of the composition (from about 49.5% to about 0.5%) must be pomalidomide. The composition in instant claim 1 weighs about 62.5 mg of which 1 mg is pomalidomide; the composition in claim 11 weighs about 125 mg of which 1 mg is pomalidomide; and the composition in claim 21 weighs about 250 mg of which 1 mg is pomalidomide; the composition in claim 31 weighs about 180 mg of which 1 mg is pomalidomide, the composition in claim 41 weighs about 240 mg of which 1 mg is pomalidomide, and the composition in claim 51 weighs about 300 mg of which 1 mg is pomalidomide; therefore the compositions in claims 1, 11, 21, 31, 41, and 51 contain pomalidomide in a concentration of about 1.6, 0.8, 0.4, 0.6, 0.4, and 0.3 wt. %, respectively, and excipients in a concentration of about 98.4, 99.2, and 99.6, 99.4, 99.6, and 99.7 wt. %, respectively, which overlap the ranges of the prior art. Furthermore, Zeldis et al. taught that

pomalidomide may be administered in an amount from about 0.1 mg to about 2 mg per day. The claimed amount of drug (1 mg) is within the range of 0.1-2 mg.

The claimed compositions contain about 56 wt. % of pre-gelatinized starch (binder). The claimed range of pre-gelatinized starch overlaps with the range of binder in the prior art 50-99 wt. %.

The claim compositions contain about 43 wt. % spray dried mannitol (filler), which is close enough to the prior art range of about 50-99 wt. %.

Zeldis et al. taught that lubricant should be present in an amount of less than 1 wt. % by weight of the composition. In the claimed compositions, sodium stearyl fumarate is present in concentrations of about 0.25 wt. %, 0.01-1 wt. %, and 0.1-0.5 wt. %, which overlap with the range of the prior art (less than 1 wt. %). The claimed concentration ranges are obvious since it has been held that in the case where the claimed ranges overlap or lie inside ranges disclosed by the prior art a *prima facie* case of obviousness exist.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed 08/16/2012 have been fully considered but they are not persuasive. In response to arguments in paragraph bridging pages 8 and 9 and first paragraph on page 9, Zeldis disclosed a method of treating lupus by administering a pomalidomide selected from pomalidomide and three other drugs. The applicant relies on Takeda court decision to rebut the finding of prima facie obviousness. The arguments are not persuasive because in Takeda the prior art reference disclosed 54 compounds that one can select from, whereas in the instant case Zeldis disclosed 4 drugs that one can select from. In the Takeda case, the selected compound was

further chemically modified, whereas in the instant case no chemical modifications occur. Furthermore, in Takeda the court decided that the prior art taught away from the selected compound, whereas in the instant case Zeldis does not criticize or teach away from using pamolidomide. Thus, one of ordinary skill in the art could envisage an oral dosage form comprising pomalidomide as the active since Zeldis disclosed pamolidomide in a list of four drugs. Zeldis taught that the dosage forms comprise suitable excipients including fillers, binders, lubricants, and disintegrants and disclosed suitable ranges of amounts of each. A person of ordinary skill in the art is capable of selecting a suitable filler, a suitable binder, a suitable lubricant, and a suitable disintegrant and use these excipients in the amounts as taught by Zeldis.

In paragraphs from bottom of page 9 to middle of 11 applicant argues that the finding of unexpected results rebuts any case of prima facie obviousness that may have been established by Zeldis. The applicant refers to instant specification pages 42-43 that show the stability for the claimed dosage forms would have been unexpected in view of the facts that those skilled in the art would have completely lacked any expectation. The arguments relating to unexpected results have been fully considered but were not found persuasive because instant specification pages 42-43 lack data that shows alleged unexpected results. The bottom of page 42 states that it was observed that the impurities in the formulation provided herein stayed negligent throughout the time period investigated, the performance characteristics of the dosage also maintained throughout the time period investigated, and the results show that the formulations provided have adequate stability for clinical and other uses. It is also not clear on what formulation was the stability tested. MPEP 716.02(b) sets forth the burden Applicant bears in establishing that alleged unexpected results are sufficient to overcome a prima facie case of obviousness, and

makes clear that the differences in results must be unexpected, unobvious, and of both statistical and practical significance. In the instant case the applicant did not show that the results were unexpected, unobvious, and of both statistical and practical significance. Applicant instead provided a conclusion that advantageous and unexpected properties were observed without showing any evidence that supports those conclusions, this however this is not sufficient to overcome obviousness.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALMA PIPIC whose telephone number is (571)270-7459. The examiner can normally be reached on 8-5 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on (571) 272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

LISTING OF CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently amended) An oral dosage form which weighs about 62.5 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides ~~1 mg~~ 0.5 mg potency of pomalidomide; 2) pregelatinized starch at an amount of 35 mg; 3) sodium stearyl fumarate at an amount of 0.16 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 62.5 mg.

2-9. (Canceled).

10. (Previously presented) The dosage form of claim 1, which is to be administered in the form of a size 4 or larger capsule.

11. (Previously presented) An oral dosage form which weighs about 125 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of pomalidomide; 2) pregelatinized starch at an amount of 70 mg; 3) sodium stearyl fumarate at an amount of 0.32 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 125 mg.

12-19. (Canceled).

20. (Previously presented) The dosage form of claim 11, which is to be administered in the form of a size 4 or larger capsule.

21. (Currently amended) An oral dosage form which weighs about 250 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides ~~1 mg~~ 2 mg potency of pomalidomide; 2) pregelatinized starch at an amount of 140 mg; 3) sodium stearyl fumarate at an amount of 0.64 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 250 mg.

22-29. (Canceled)

30. (Previously presented) The dosage form of claim 21, which is to be administered in the form of a size 2 or larger capsule.

31. (Currently amended) An oral dosage form which weighs about 180 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides ~~1 mg~~ 3 mg potency of pomalidomide; 2) pregelatinized starch at an amount of 100.8 mg; 3) sodium stearyl fumarate at an amount of 0.45 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 180 mg.

32-39. (Canceled)

40. (Previously presented) The dosage form of claim 31, which is to be administered in the form of a size 2 or larger capsule.

41. (Currently amended) An oral dosage form which weighs about 240 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides ~~1 mg~~ 4 mg potency of pomalidomide; 2) pregelatinized starch at an amount of 134.4 mg; 3) sodium stearyl fumarate at an amount of 0.6 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 240 mg.

42-49. (Canceled).

50. (Previously presented) The dosage form of claim 41, which is to be administered in the form of a size 2 or larger capsule.

51. (Currently amended) An oral dosage form which weighs about 300 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides ~~1 mg~~ 5 mg potency of pomalidomide; 2) pregelatinized starch at an amount of 168 mg; 3) sodium stearyl fumarate at an amount of 0.75 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 300 mg.

52-59. (Canceled)

60. (Previously presented) The dosage form of claim 51, which is to be administered in the form of a size 1 or larger capsule.

61. (Previously presented) An oral dosage form in the form of a capsule which comprises: 1) pomalidomide at an amount of 0.1 to 3 weight percent of the total weight of the composition; 2) a binder or filler at an amount of 90 to 99 weight percent of total weight of the composition, wherein the binder or filler is starch, mannitol or a mixture thereof.

62. (Previously presented) The oral dosage form of claim 61, wherein pomalidomide is present at an amount of 0.5 to 2 weight percent of total weight of the composition.

63. (Previously presented) The oral dosage form of claim 61, wherein the binder or filler is present at an amount of 95 to 99 weight percent of total weight of the composition.

64. (Previously presented) The oral dosage form of claim 61, wherein the binder or filler is a mixture of starch and mannitol.

65. (Previously presented) The oral dosage form of claim 64, wherein the starch is ~~pregleatinized~~ pregelatinized starch.

66. (Previously presented) The oral dosage form of claim 64, wherein the mannitol is spray dried mannitol.

67. (Previously presented) The oral dosage form of claim 61 further comprising a lubricant at an amount of 0.01 to 1 weight percent of total weight of the composition.

68. (Previously presented) The oral dosage form of claim 67, wherein the lubricant is present at an amount of 0.1 to 0.5 weight percent of total weight of the composition.

69. (Previously presented) The oral dosage form of claim 67 or 68, wherein the lubricant is sodium stearyl fumarate.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/783,390	**Applicant(s)** TUTINO ET AL.
	Examiner ALMA PIPIC	**Art Unit** 1617

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 February 2013 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☐ will not be entered, or (b) ☒ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

STATUS OF CLAIMS

14. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed: .
    Claim(s) objected to: .
    Claim(s) rejected: 1,10,11,20,21,30,31,40,41,50,51 and 60-69.
    Claim(s) withdrawn from consideration: .

/RICHARD SCHNIZER/
Primary Examiner, Art Unit 1635

Continuation of 5. Applicant's reply has overcome the following rejection(s): Rejection of claims 1, 10, 21, 30, 31, 40, 41, 50, 51, and 60 under 35 USC § 112, 1st Paragraph.

Continuation of 11. does NOT place the application in condition for allowance because: Arguments presented on 2/13/2013 have not been found persuasive as explained below and claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, and 60-69 would be rejected in the following way:

Claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, and 60 remain rejected under 35 USC § 112, 2nd Paragraph.
Arguments directed to the rejections of claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, and 60 under 35 USC § 112, 2nd Paragraph filed 02/13/2013 (page 7-8, item E) have been fully considered but were not found persuasive because potency was not redefined by the specification and it is given its plain and ordinary meaning. Potency is a measure of an amount of drug necessary to produce an effect of a given magnitude. In the instant case the effect and the magnitude of the said effect are unknown and thus the amount of pamolidamide required to give a potency of 1 mg cannot be determined since it remains unknown what effect one is trying to achieve. A 1 mg of a drug will have different effect on a mouse in comparison to an effect it has on an adult human. Since the subject and the effect that one is trying to achieve on the subject are unknown, one cannot determine the amount of pomalidomide that would product 1 mg worth of potency. Based on the specification (from page 9 line 30 to page 10 line 5) it appears that the applicant intended to say that since pomalidomide is obtained at a purity of less than 100%, the amount of impure pamolidomide that is utilized in the dosage forms should provide a specified amount of pure pamolidomide such as 0.5 mg. Thus, the terms "0.5 mg potency", "1 mg potency", "2 mg potency", "3 mg potency", "4 mg potency", and "5 mg potency" render the claims indefinite and for the purpose of applying prior art the claims are interpreted as requiring 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg of pamolidomide.

Claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, 60, and 61-69 as amended would be rejected under 35 U.S.C. 103(a) as being unpatentable over Zeldis et al. (Pub. No. US 2007/0155791 A1, Published July 5, 2007 - of record in PTO-892 dated 04/24/2012) in view of Remington's Pharmaceutical Sciences (17th Edition, Published 1985, Pages 1613-1615 and 1625-1626 - of record in PTO-892 dated 04/24/2012) and McNally et al. (Patent No. 5,593,696 Date of Patent January 14, 1997 - of record in PTO-892 dated 04/24/2012).
Claim 1 encompasses an oral dosage form which weighs about 62.5 mg and comprises: 1) pomalidomide in an amount of 0.5 mg; 2) pregelatinized starch in an amount of 35 mg; 3) sodium stearyl fumarate in an amount of 0.16 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 62.5 mg.
Claim 11 encompasses an oral dosage form which weighs about 125 mg and comprises: 1) pomalidomide in an amount of 1 mg; 2) pregelatinized starch in an amount of 70 mg; 3) sodium stearyl fumarate in an amount of 0.32 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 125 mg.
Claim 21 encompasses an oral dosage form which weighs about 250 mg and comprises: 1) pomalidomide in an amount of 2 mg; 2) pregelatinized starch in an amount of 140 mg; 3) sodium stearyl fumarate in an amount of 0.64 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 250 mg.
Claim 31 encompasses an oral dosage form which weighs about 180 mg and comprises: 1) pomalidomide in an amount of 3 mg; 2) pregelatinized starch in an amount of 100.8 mg; 3) sodium stearyl fumarate in an amount of 0.45 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 180 mg.
Claim 41 encompasses an oral dosage form which weighs about 240 mg and comprises: 1) pomalidomide in an amount of 4 mg; 2) pregelatinized starch in an amount of 134.4 mg; 3) sodium stearyl fumarate in an amount of 0.6 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 240 mg.
Claim 51 encompasses an oral dosage form which weighs about 300 mg and comprises: 1) pomalidomide in an amount of 5 mg; 2) pregelatinized starch in an amount of 168 mg; 3) sodium stearyl fumarate in an amount of 0.75 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 300 mg.
Claim 61 encompasses an oral dosage form in the form of a capsule which comprises: 1) pomalidomide at an amount of 0.1 to 3 weight percent of the total weight of the composition; 2) a binder or filler at an amount of 90 to 99 weight percent of total weight of the composition, wherein the binder or filler is starch, mannitol or a mixture thereof. Dependent claim 62 requires pomalidomide at an amount of 0.5 to 2 weight percent of total weight of the composition. Dependent claim 63 requires the binder or filler at an amount of 95 to 99 weight percent of total weight of the composition. Dependent claims 64-66 require that the binder or filler is a mixture of starch and mannitol, wherein the starch is pregelatinized starch and mannitol is spray dried mannitol. Depended claims 67-69 require a lubricant at an amount of 0.01 to 1 weight percent and 0.1 to 0.5 weight percent of the total weight of the composition, wherein the lubricant is sodium stearyl fumarate.

The teachings of Zeldis et al. are related to methods for treating lupus and compositions comprising 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione (e.g. pomalidomide) (Abstract). In one embodiment pomalidomide is administered daily at a dose of from about 0.1 to 5 mg per day (Paragraph 0096). In one embodiment, pomalidomide can be administered in an amount from about 0.1 to about 100 mg. In a particular embodiment polamidomide may be administered in an amount of from about 0.1 to about 2 mg per day, or from 0.1 to about 5 mg every other day (Paragraph 0102). Typical dosage forms comprise pomalidomide in an amount from about 0.1 to about 150 mg (Paragraph 0106). Single unit dosage forms are suitable for oral administration, including capsules (Paragraph 0109). The composition and type of dosage form will vary depending on its use. For example, a dosage form used in the acute treatment of a disease may contain larger amount of active ingredient than a dosage form used in the chronic treatment of the same disease (Paragraph 0110). Typical dosage forms comprise excipients (Paragraph 0111). Oral dosage forms, such as capsules, contain a predetermined amount of active ingredients and can be prepared by methods well known in the art (Paragraph 0118). Excipients suitable for use in solid oral dosage forms include starches, sugars, diluents, lubricants, and binders (Paragraph 0119). Pre-gelatinized starch is an example of binder (Paragraph 0122). Suitable fillers include mannitol and pre-gelatinized starch and mixtures thereof. The binder or filler in pharmaceutical composition is typically present in from about 50 to about 99 wt. % of the dosage from (Paragraph 0124). The compositions comprise from about 0.5 to about 15 wt. % disintegrants (Paragraph 0125).
Although Zeldis et al. taught mannitol as excipient, they are silent whether or not it is spray-dried mannitol.
Remington's discloses that direct compression for tablets containing less than 25% of drug substance can be used by formulation with a suitable diluent which acts as a carrier (Page 1614, Left Column, First Paragraph). Among the spray-dried materials available for direct

compression formulas are lactose, mannitol and flour (Page 1615, Left Column, First Paragraph). Spray-drying is more economical than other processes since it produces a dry powder directly from a liquid and eliminates other processing steps. By the elimination of additional steps, labor, equipment cost, space requirements, and possible contamination of the product are reduced (Page 1615, Left Column, Third Paragraph).
Although Zeldis et al. taught that the oral dosage forms are advantageously administered in capsule form, they are silent regarding capsule sizes that should be utilized.
Remington's discloses various capsule sizes (Page 1625, Right Column, Fig. 90-30). The capsules are numbered from 000, the largest size which can be swallowed, to 5, which is the smallest. The approximate capacity for capsules from 000 to 5 ranges from 600 mg to 30 mg, although this will vary because of the different densities of powdered drug material (Page 1626, Left Column, First Paragraph) (Relevant to claims 10, 20, 30, 40, 50, and 60).
Although Zeldis taught incorporating lubricants such as magnesium stearate, calcium stearate, stearic acid, and talc in an amount of less than 1% by weight of the composition (paragraph 0127), they do not teach lubricant sodium stearyl fumarate.
The teachings of McNally et al. are relied upon to show that sodium stearyl fumarate is a known lubricant in the art, and that it is an art recognized equivalent of magnesium stearate, calcium stearate, stearic acid, and talc in oral pharmaceutical dosage forms (Column 4, lines 27-32). The teachings of McNally et al. are related to oral dosage forms (Abstract).

A person of ordinary skill in the art would have been motivated to combine the teachings of Zeldis et al., McNally et al., and Remington's because they are related to oral dosage forms that contain an active agent and excipients. It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to have followed the teachings of Zeldis and made oral dosages in the form of capsules comprising 0.1-5 mg of pamolidomide as the active, a mixture of pre-gelatinized starch and mannitol as filler and binder, and lubricant in order to form a dosage form suitable for treatment of a chronic disease, with a reasonable expectation of success because Zeldis taught oral dosage forms comprising those components and suggested using an amount of the active in the lower end of the range in order to treat a chronic disease. It would have been obvious to have selected a mixture of pre-gelatinized starch and mannitol as filler and binder because Zeldis taught that they are suitable for that use. It would have been obvious to have modified Zeldis' oral dosage forms by substituting lubricants magnesium stearate, calcium stearate, stearic acid, or talc with sodium stearyl fumarate, with a reasonable expectation of success because sodium stearyl fumarate, magnesium stearate, calcium stearate, stearic acid, and talc are recognized in the art as equivalent lubricants in oral dosage forms according to McNally et al. A person of ordinary skill would have been motivated to use spray dried mannitol because Remington's discloses that spray drying of excipients is more economical than other processes since it produces a dry powder directly from a liquid and eliminates other processing steps. By the elimination of additional steps, labor, equipment cost, space requirements, and possible contamination of the product are reduced. It would have been obvious to make single unit dosage forms that contain predetermined amounts of active, with a reasonable expectation of success because Zeldis et al. taught discrete single unit dosage forms that contain predetermined amounts of drug in the range from about 0.1 mg to about 5 mg. A person of ordinary skill in the art is capable of determining appropriate quantities of drug per dosage form depending on its intended use and the quantity of drug that is required to treat a particular patient as well as amounts of suitable excipients. The claimed ranges of pomalidomide, pre-gelatinized starch, and sodium stearyl fumarate are obvious over Zeldis et al. in view of McNally and Remington's since it has been held where the claimed ranges overlap or lie inside ranges disclosed by the prior art a prima facie case of obviousness exist (MPEP 2144.05(I)). The claimed amount of spray dried mannitol (about 43 wt. %) is obvious over the prior art range (about 50-99 wt. %) since it has been held that a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties (MPEP 2144.05(I)). It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to have made the dosage forms of Zeldis et al. in the capsule form using the capsule sizes disclosed by Remington's, with a reasonable expectation of success because Remington's discloses capsule capacities and sizes that are used to deliver pharmaceuticals. One of ordinary skill would have been able to determine which capsule size is appropriate for a particular dosage amount (e.g. smaller capsule size for a small dosage, larger capsule size for a large dosage) because Remington's provides capsule capacities as ranging from 30 mg to 600 mg. The claimed weights of dosage forms 62.5 mg, 125 mg, 250 mg, 180 mg, 240 mg, and 300 mg are obvious over Remington's because they overlap with the range of amounts (30-600 mg) that the standard size capsules are capable of holding. One of ordinary skill is capable of determining the weight of a dosage form that is suitable for a particular capsule size.

Regarding claims 1, 11, 21, 31, 41, 51, 61-63, 67, and 68, Zeldis et al. taught that typical dosage forms contain from about 50% to about 99% of fillers or binders, from about 0.5 to about 15 wt. % disintegrant, and less than 1 wt. % lubricant. Therefore, the remainder of the composition (from about 49.5% to about 0.5%) must be pomalidomide. The composition in instant claim 1 weighs about 62.5 mg of which 0.5 mg is pomalidomide; the composition in claim 11 weighs about 125 mg of which 1 mg is pomalidomide; the composition in claim 21 weighs about 250 mg of which 2 mg is pomalidomide; the composition in claim 31 weighs about 180 mg of which 3 mg is pomalidomide, the composition in claim 41 weighs about 240 mg of which 4 mg is pomalidomide, and the composition in claim 51 weighs about 300 mg of which 5 mg is pomalidomide; therefore the compositions in claims 1, 11, 21, 31, 41, and 51 contain pomalidomide in a concentration of about 0.8, 0.8, 0.8, 1.7, 1.7, and 1.7 wt. %, respectively, and excipients in a concentration of about 99.2, 99.2, 99.2, 98.3, 98.3, and 98.3 wt. %, respectively, which overlap the ranges of the prior art. Furthermore, Zeldis et al. taught that pomalidomide may be administered in an amount from about 0.1 mg to about 5 mg per day. The claimed amounts of drug (0.5, 1, 2, 3, 4, and 5 mg) are within the range of 0.1-5 mg.
The claimed compositions contain about 56 wt. % of pre-gelatinized starch (binder). The claimed range of pre-gelatinized starch overlaps with the range of binder in the prior art 50-99 wt. %.
The claim compositions contain about 43 wt. % spray dried mannitol (filler), which is close enough to the prior art range of about 50-99 wt. %.
Zeldis et al. taught that lubricant should be present in an amount of less than 1 wt. % by weight of the composition. In the claimed compositions, sodium stearyl fumarate is present in concentrations of about 0.25 wt. %, 0.01-1 wt. %, and 0.1-0.5 wt. %, which overlap with the range of the prior art (less than 1 wt. %). The claimed concentration ranges are obvious since it has been held that in the case where the claimed ranges overlap or lie inside ranges disclosed by the prior art a prima facie case of obviousness exist.

Examiner's Response to Applicant's Arguments
Applicant's arguments filed 02/13/2013 (Pages 8-10, Item F) have been fully considered but they are not persuasive. In response to arguments in paragraph bridging pages 8 and 9, Zeldis taught limited lists of various excipients. A list of 26 binders is considered a limited list (Zeldis at paragraphs 0122 and 0123). A list of 11 fillers is considered a limited list (Zeldis at paragraph 0124). A list of 15 disintegrants is considered a limited list (Zeldis at paragraph 0126). A list of 27 lubricants is considered a limited list (Zeldis at paragraph 0127). Zeldis taught oral dosage forms containing discrete amounts of pamolidomide wherein the amounts of pamolidomide from 0.1 to 5 mg. As described above in the rejection, the claimed amounts of pamolidomide and excipients are obvious over Zeldis' amounts of pamolidomide and excipients because they overlap. Zeldis taught that the dosage forms comprise suitable excipients including fillers, binders, lubricants, and disintegrants and disclosed suitable ranges of amounts of each. A person of ordinary skill in the art is capable of selecting a suitable filler, a suitable binder, a suitable lubricant, and a suitable disintegrant and use these excipients in the amounts as taught by Zeldis. Arguments directed to Remington and McNally (page 9, second paragraph) only recite that they do not cure the deficiencies of Zeldis. This has not been found persuasive because arguments directed to Zeldis have not been found persuasive.
Arguments in the paragraph bridging pages 9-10 have not been found persuasive because Zeldis provided limited lists of excipients and selection of pregelatinized starch and mannitol from those limited lists is not excessive picking and choosing. Substituting the lubricant magnesium stearate with its art recognized equivalent sodium stearyl fumarate is not considered picking and choosing. MPEP 2144.06 states "An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In reFout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."
In the second paragraph on page 10 Applicant argues that the finding of unexpected results. The applicant refers to instant specification pages 42-43 that show the stability for the claimed dosage forms would have been unexpected in view of the facts that those skilled in the art would have completely lacked any expectation. Applicant argues that the specification at page 42 to 43 provides data showing that the claimed oral dosage forms have been found to have stability for clinical use up to 24 months and that prior to this application the formulations containing pamolidomide tested and used by Applicants had stability of about 1 month maximum. The arguments relating to unexpected results have been fully considered but were not found persuasive because the instant specification pages 42-43 lack data that shows alleged unexpected results. The substitute specification dated 08/16/2012 shows dosage formulation examples 4, 5, and 6 on pages 42-43, and on the bottom of page 43 the section on stability of formulations begins. Therefore the substitute specification does not discuss nor provide data showing unexpected results. Pages 42-43 in specification dated 05/19/2010 discuss the stability of formulation (Example 7) at 1, 3, and 6 months, however there are no data of this study. The bottom of page 42 states that it was observed that the impurities in the formulation provided herein stayed negligent throughout the time period investigated, the performance characteristics of the dosage also maintained throughout the time period investigated, and the results show that the formulations provided have adequate stability for clinical and other uses. Furthermore, it is unknown what formulation was tested in the stability study. There is nothing in the specification that shows the comparison of the stability of the claimed dosage forms to those of the prior art. It is unclear where the Applicant is getting the alleged data that the claimed formulation is stable up to 24 months and the prior art formulations are stable up to 1 month. MPEP 716.02(b) sets forth the burden Applicant bears in establishing that alleged unexpected results are sufficient to overcome a prima facie case of obviousness, and makes clear that the differences in results must be unexpected, unobvious, and of both statistical and practical significance. In the instant case the applicant did not show that the results were unexpected, unobvious, and of both statistical and practical significance. Applicant instead provided a conclusion that advantageous and unexpected properties were observed without showing any evidence that supports those conclusions, this however this is not sufficient to overcome obviousness.

Withdrawn Claim Objections
Objections to the claims listing and claim 65 have been obviated with the claim amendment dated 02/13/2012.

LISTING OF CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently amended) An oral dosage form in the form of a capsule which weighs ~~about~~ 62.5 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 0.5 mg ~~potency~~ of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 35 mg; 3) sodium stearyl fumarate at an amount of 0.16 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 62.5 mg.

2-9. (Canceled).

10. (Previously presented) The dosage form of claim 1, which is to be administered in the form of a size 4 or larger capsule.

11. (Currently amended) An oral dosage form in the form of a capsule which weighs ~~about~~ 125 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg ~~potency~~ of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 70 mg; 3) sodium stearyl fumarate at an amount of 0.32 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 125 mg.

12-19. (Canceled).

20. (Previously presented) The dosage form of claim 11, which is to be administered in the form of a size 4 or larger capsule.

21. (Currently amended) An oral dosage form in the form of a capsule which weighs ~~about~~ 250 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 2 mg ~~potency~~ of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 140 mg; 3) sodium stearyl fumarate at an amount of 0.64 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 250 mg.

22-29. (Canceled)

30. (Previously presented) The dosage form of claim 21, which is to be administered in the form of a size 2 or larger capsule.

31. (Currently amended) An oral dosage form in the form of a capsule which weighs ~~about~~ 180 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 3 mg ~~potency~~ of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 100.8 mg; 3) sodium stearyl fumarate at an amount of 0.45 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 180 mg.

32-39. (Canceled)

40. (Previously presented) The dosage form of claim 31, which is to be administered in the form of a size 2 or larger capsule.

41. (Currently amended) An oral dosage form in the form of a capsule which weighs ~~about~~ 240 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 4 mg ~~potency~~ of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 134.4 mg; 3) sodium stearyl fumarate at an amount of 0.6 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 240 mg.

42-49. (Canceled).

50. (Previously presented) The dosage form of claim 41, which is to be administered in the form of a size 2 or larger capsule.

51. (Currently amended) An oral dosage form in the form of a capsule which weighs ~~about~~ 300 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 5 mg ~~potency~~ of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 168 mg; 3) sodium stearyl fumarate at an amount of 0.75 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 300 mg.

52-59. (Canceled)

60. (Previously presented) The dosage form of claim 51, which is to be administered in the form of a size 1 or larger capsule.

61. (Previously presented) An oral dosage form in the form of a capsule which comprises: 1) pomalidomide at an amount of 0.1 to 3 weight percent of the total weight of the composition; 2) a binder or filler at an amount of 90 to 99 weight percent of total weight of the composition, wherein the binder or filler is starch, mannitol or a mixture thereof.

62. (Previously presented) The oral dosage form of claim 61, wherein pomalidomide is present at an amount of 0.5 to 2 weight percent of total weight of the composition.

63. (Previously presented) The oral dosage form of claim 61, wherein the binder or filler is present at an amount of 95 to 99 weight percent of total weight of the composition.

B. The Rejection Under 35 U.S.C. § 112, 2nd Paragraph Should be Withdrawn

On page 3 of the Office Action, and page 2 of the Advisory Action, claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51 and 60 are rejected as allegedly indefinite. Specifically, it is alleged that claims 1, 11, 21, 31, 41, and 51 are indefinite because "they recite potency of pomalidomide in milligrams. Potency of a drug is expressed in International Units (IU) and not mass." (Office Action, page 3).

Although Applicants respectfull disagree with this assertion, especially for the reasons set forth in Applicants' responses dated August 16, 2012 and February 13, 2013, claims 1, 11, 21, 31, 41 and 51 are amended solely to expedite the prosecution of the current application. Specifically, the claims are amended to recite that the amount of pomalidomide, or a pharmaceutically acceptable salt thereof, in the claimed dosage forms is "an amount that provides [specified mg anount] of 100% pure pomalidomide." (See claims 1, 11, 21, 31, 41 and 51). As the claims recite the amount of pomalidomide strictly in terms of amount, and do not recite any potency, Applicants respectfully request that this rejection be withdrawn.

C. The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

On pages 6-13 of the Office Action, claims 1, 10, 11, 20, 21, 30, 31, 40, 21, 50, 51, 60 and 61-69 are rejected as allegedly obvious over Zeldis *et al.*, U.S. Pub. No. 2007/0155791 ("Zeldis") in view of Remington's Pharmaceutical Sciences, 17th Edition, published 1985, pages 1613-1615 and 1625-1626 ("Remington") and McNally *et al.* U.S. Patent No. 5,593,696 ("McNally"). The Examiner alleges that "it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have followed the teachings of Zeldis and made oral dosages in the form of capsules comprising…pomalidomide as the active, a mixture of pre-gelatinized starch and mannitol as filler and binder, and lubricant…with a reasonable expectation of success because Zeldis taught oral dosage forms comprising these components and suggested using an amount of the active in the lower end of the range to treat a chronic disease." (Office Action, page 10). Applicants respectfully disagree and traverse this rejection.

First, Applicants respectfully reiterate that the combnation of Zeldis, Remington and McNally cannot render the currently claimed dosage forms obvious because there simply is no disclosure in the cited references that would have prompted one skilled in the art to prepare a

composition having pomalidomide at the specified amounts, along with the particular binders and fillers at the specified amounts as recited by claims 1, 11, 21, 31, 41 and 51. Likewise, with regard to the new claim 61, there is no disclosure in the cited referencews that having pomalidomide at the specific mass percent range recited by the presently amended claims in combination with the specific binders and fillers, would result in compositions with advantageous properties. These arguments were set forth more fully in Applicants' previous response dated February 13, 2013, which is incorporated herein in its entirety by reference.

Second, it is respectfully pointed out that there are other reasons that would render the claimed dosage forms unobvious over the cited references. For instance, as discussed during the in –person interview, the inventors came across unexpected and unforeseen issues in arriving at the claimed dosage forms. Applicants respectfully invite the Examiner's attention to the declaration by Mr. Anthony Tutino ("Declaration"), submitted herewith as **Exhibit A**. As explained in detail in the Declaration, as is commonly practiced in the field, the formulation study began with initial 1:1 compatability tests between the API (*i.e.*, pomalidomide) and various commonly used excipients such as anhydrous dibasic calcium phosphate, lactose anhydrous, corn starch, pregelatinized starch, microcrystalline cellulose, spray dried mannitol, croscarmellose sodium, sodium starch glycolate, sodium starch fumarate, and magnesium stearate. (Declaration, ¶6). From the testing, it was found that pomalidomide is compatible with each of those excipients tested. (*Id.*).

As Mr. Tutino indicates, the 1:1 compatibility tests is designed to provide the indication as to whether a particular excipient would be compatable with the API being formulated, and as such, once the excipients are found compatible from the 1:1 compatibility tests, it is commonly expected that a formulation using those excipients would not present a compatibility problem. (*Id.*, ¶5). However, contrary to this expectation, it was found that many of the formulations lack sufficient stability. (*Id.*, ¶8). Not only was this unexpected, it also shows that not just any excipients (for example, those listed in the extensive list of excipients provided in Zeldis) can be combined to provide the favorable stability exhibited by the currently claimed dosage forms. Based on this result alone, Applicants respectfully submit that picking and choosing of the excipients recited by the current claims from the extensive list of excipients provided in Zeldis would clearly not have been possible without the aid of an impermissible hindsight.

Furthermore, it is noted that the only example in the primary reference Zeldis that provides a capsule formulation is Example 8. Aside from the fact that the formulation provided in that example is merely prophetic, the formulation contains a significant amount of microcrystalline cellulose. In this regard, it is resepectfully pointed out that the Zeldis formulation, even if it were not prophetic, would be expected to lack the stability possessed by the currently claimed dosage forms based on information learned during the development of the currently claimed dosage forms. (Declaration, ¶11). Specifically, a formulation containing microcrystalline cellulose was tested during the development. (*Id.*). While the formulation passed the compatibility testing, it was found that the formulation was not stable beyond 3 months period. (*Id.*). As the degradation of pomalidomide caused by hydrolysis, and as the other excipients in the tested formulation did not contain water, the stability issue observed in that formulation was attributed to the presence of microcrystalline cellulose, which has an LOD of approximately 5%. (*Id.*, ¶12). As the formulation provided in the prophetic Example 8 of Zeldis contains a significant amount of microcrystalline cellulose, it is expected that the formulation would have a stability problem similar to that observed for the developmental formulation described above.

In sum, the data clearly show that randomly picking any excipients from the list of excipients provided in Zeldis would not have achieved the stability possessed by the currently claimed pomalidomide dosage forms. Fruther, it was shown that the only concrete (*albeit* prophetic) capsule formulation provided in Zeldis would also likely have stability problem. In view of these, it is respectfully pointed out that Zeldis, alone or in combination with Remington and McNaly, could not have provided any teaching or suggestion to lead those skilled in the art to the currently claimed dosage forms, which contain specific excipients at specific amounts to provide favorable stability required for clinical use.

In this regard, it appears that the unexpected and superior stability data referred to by Applicants in their previous response is not recognized in the Office Action. Presumably, this is because the Office belives that the conclusion of stability provided in plain sentences, without showing numerical or figural data, is not sufficient. (Advisory Action, pgae 4). Although Applicants respectfully disagree with this assessment, especially for the fact that the assertion of stability made in the specification should be presumed to be valid and correct, the numerial data regarding stability, in terms of the level of impurities observed at specified time points, are provided in the Declaration. In view of this, Applicants respectfully submit that the unexpected

benefit of the currently claimed dosage forms should be recognized, and any presumption of obviousness that may have been estabilished by Zeldis, Remington and McNaly should be rebutted.

D. Conclusion

For at least the reasons discussed above, Applicants respectfully submit that all of the pending claims are in allowable form, and thus respectfully request that their rejections be withdrawn.

No fee is believed to be due with this paper. However, if fees are required for the submission of this paper, or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013 (referencing 501872-999831).

Respectfully submitted,

Date: June 17, 2013

/Hoon Choi/

Hoon Choi Reg. No. 64,214

for: Anthony M. Insogna Reg. No. 35,203

JONES DAY
12265 El Camino Real
Suite 200
San Diego, CA 92130
(858) 314-1200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Tutino *et al.*	Confirmation No.: 6628
Application No.: 12/783,390	Group Art Unit: 1617
Filed: May 19, 2010	Examiner: Pipic, Alma
For: Formulations of 4-Amino-2-(2,6-Dioxopiperidine-3-yl)isoindoline-1,3-dione	Attorney Docket No.: 9516-831-999 (CAM No.: 501872-999831)

DECLARATION BY ANTHONY TUTINO

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Anthony Tutino, declare and state that:

1. I received my Bachelor of Science degree in Pharmaceutical Sciences from Saint John's University, New York. I hold licenses in the practice of Pharmacy from New York and New Jersey. I also received a Certification in Project Management from The George Washington University, Washington, D.C.

2. From 1984 to 1996, I was with Sandoz Pharmaceuticals, lastly as the Associate Director of Technology Development. From 1997 to 2004, I was a Director of Process Development at Novartis Pharmaceutical. From 2004 to present, I have been with Celgene Corporation, Summit, NJ, the assignee of the current application, currently as the Executive Director of Global Pharmaceutical Development and Technology. I am a named inventor of the above-identified application.

3. I am familiar with the disclosure and claims of the current patent application. I understand that the pending claims recite, *inter alia*, pharmaceutical compositions of pomalidomide consisting of specific amounts of pomalidomide and specific amounts of pregelatinized starch, sodium stearyl fumarate and spray dried mannitol. I have reviewed the Office Action and references cited in the Office Action.

4. I understand that one of the issues is whether it would have been plausible for one skilled in the art to pick the particular excipients recited by the current claims from the list of excipients provided in U.S. Publication No. 2007/0155791 by Zeldis *et al.* ("Zeldis"). It is my opinion that one would not have been able to arrive at the dosage forms recited by the current claims based simply on the references cited in the Office Action for at least the following reasons.

5. In developing pharmaceutical formulations, a common practice is to start with 1:1 compatibility tests between active pharmaceutical ingredient ("API") and various commonly used excipients. In short, the 1:1 compatibility test involves combining the active ingredient with an excipient in a ratio that would normally be found in a formulated dosage product. These mixtures are then placed at stress conditions (high temperature and high humidity) and tested at regular intervals to determine if any degradation of the active ingredient is taking place. The test is designed to provide insight as to whether an excipient would be compatible with the API being formulated, and as such, once certain excipients are found compatible with API from the tests, it is expected that a formulation using those excipients would not present a compatibility problem.

6. Thus, in developing the pomalidomide formulations, 1:1 compatibility tests have been conducted between pomalidomide and various candidate excipients. The tested excipients included anhydrous dibasic calcium phosphate, lactose anhydrous, corn starch, pregelatinized starch, microcrystalline cellulose, spray dried mannitol, croscarmellose sodium, sodium starch glycolate, sodium starch fumarate, and magnesium stearate. From the testing, it was found that pomalidomide is compatible with each of those excipients tested.

7. Based on that result, various test formulations were made using the excipients that were found to be compatible with pomalidomide. The components of the tests formulations are shown below:

Ingredient	Function	Formulation (Quantity per blend, %)									
		A	B	C	D	E	F	G	H	I	J
CC-4047 (Process B)	Active ingredient	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40
Anhydrous dibasic calcium phosphate	Bulking agent	45.35		95.35	45.35	45.35		45.35	45.35	45.35	
Spray dried mannitol	Bulking agent						45.35				
Pregelatinized starch	Bulking agent	50.00	95.35		54.00	50.25	50.00		50.00	50.00	
Starch (corn starch and pregelatinized)	Bulking agent							50.00			
Lactose anhydrous	Bulking agent										75.00
Microcrystalline cellulose	Bulking agent										20.60
Croscarmellose sodium	Disintegrant	4.00	4.00	4.00		4.00	4.00	4.00		4.00	4.00
Sodium starch glycolate	Disintegrant								4.00		
Sodium stearyl fumarate	Lubricant	0.25	0.25	0.25	0.25		0.25	0.25	0.25		
Magnesium stearate	Lubricant									0.25	1.00

8. To my surprise, it was found that Formulations A, C, E, G, H and I above were found to present a compatibility problem, *i.e.*, were unstable after two weeks storage. This was unexpected because I would have expected that compatibility issues would not exist based on the 1:1 compatibility tests preliminarily conducted for each of the excipients contained in those formulations. Consequently, it is my opinion that one reading Zeldis could not have just picked and chosen random excipients from the list of excipients provided in that reference and arrive at a formulation that does not exhibit this compatibility problem.

9. Next, Formulations D, F and J, which did not have the compatibility issues, were further advanced for testing on long term stability. After six months of storage at the accelerated condition (40°C/75% RH) and 12 months at the ambient condition (25°C/60% RH), the formulations were tested for relative impurity levels. The results were as follows:

Timepoint			T0	1 month	3 months	6 months			9 months	12 months
Conditions °C/%RH				40/75	25/60	40/75	25/60	40/75	25/60	25/60
Strength (mg)	Formulation	Impurity	Relative Impurity (%)							
1	D	Impurity A	0.02	0.27	0.14	0.46	X	X	X	X
		Impurity B	0.00	0.04	0.02	0.13	X	X	X	X
	F	Impurity A	0.01	0.00	0.00	0.01	0.03	0.05	0.01	0.01
		Impurity B	0.00	0.01	0.00	0.00	0.01	0.02	0.00	0.00
	J	Impurity A	0.55	0.15	0.44	0.64	X	X	X	X
		Impurity B	0.00	0.01	0.00	0.00	X	X	X	X
5	D	Impurity A	0.02	0.19	0.09	0.32	X	X	X	X
		Impurity B	0.00	0.07	0.02	0.12	X	X	X	X
	F	Impurity A	0.01	0.00	0.00	0.01	0.00	0.01	0.01	0.00
		Impurity B	0.00	0.01	0.00	0.00	0.00	0.01	0.00	0.00

10. In the table above, the denotation "X" indicates that no further study was conducted to the batch beyond the specified period due to high level of impurities. As can be seen from the above, only Formulation F, *i.e.*, formulation claimed in this application, was shown to be stable beyond 3 months period. It is my opinion that this further shows that it would have been impossible for one reading Zeldis and other references cited in the Office Action would arrive at the currently claimed dosage forms without specifically knowing that the particular combination of the particular excipients recited by the current claims would provide a formulation having favorable compatibility and stability properties.

11. With regard to the prophetic formulation described in Example 8 of the Zeldis, it is my opinion that the formulation, even if actually made, would not possess the advantageous stability profile possessed by the currently claimed dosage forms. This is because Formulation J, a candidate formulation tested during the development of the current dosage forms, which contained a significant amount of microcrystalline cellulose, did not have the advantageous stability exhibited by the currently claimed dosage forms. (*See* Table above, Formulation F in comparison with Formulation J).

12. The degradation of pomalidomide is caused by hydrolysis. In Formulation J, none of the excipients, other than microcrystalline cellulose, contained available, unbound water. Therefore, the stability issue observed in that formulation was attributed to the presence of microcrystalline cellulose, which has a loss on drying (LOD – measure of water content) of approximately 5%. As the formulation provided in Example 8 of Zeldis also contains a significant amount of microcrystalline cellulose (and thus, water), I would expect that the Zeldis formulation would exhibit an unfavorable stability issue similar to that exhibited by Formulation J.

13. I, Anthony Tutino, declare that all statements made herein are of my own knowledge to be true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent that may issue there from.

Dated: 14 June 2013

ANTHONY TUTINO, R.Ph.